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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/402,636	04/26/2000	Richard B. Mazess	17620-9277	6232

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EXAMINER
HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
1644	18

DATE MAILED: 04/09/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/402,636	MASCAX ET AL.	
	Examiner	Art Unit	
	" Neon" Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9,11,17,18 and 20-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9,11,17,18 and 20-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The request filed on 1/31/02 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/402,636 is acceptable and a CPA has been established. An action on the CPA follows.

2. Claims 1-7, 9, 11, 17-18 and 20-22 are pending and are being acted upon.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-7, 9, 11, 17-18 and 20-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification as filed discloses only a conjugate comprising at least one vitamin D moiety associated with a target molecule moiety having an affinity for a tissue of interest wherein the vitamin D moiety has a formula II as shown on page 11 lines 13-19 bridging page 12 lines 1 to 6 of the specification, wherein said moiety is selected from the group consisting of 1α previtamin D, 1α, 24-$(OH)_2$D2-aminoalkyl, 11α, 25-$(OH)_2$D2-aminoalkyl linked to the hydroxyl group at C-1, C-3, C-24 and C-25 of said vitamin D moiety and wherein the targeting moiety is bisphosphonate.

The specification does not reasonably provide a **written description** of *any* conjugate comprising *any* "vitamin D moiety" associated with *any* target molecule moiety having an affinity for a tissue of interest. There is insufficient written description about the **structure** associated with function of any "vitamin D moiety" and *any* "targeting molecule moiety". Applicant discloses only six conjugates having one targeting moiety such as bisphosphonate linked to the hydroxyl group at C-1, C-3, C-24 and C-25 of said vitamin D such as 1α, 24-$(OH)_2$D2-aminoalkyl, 11α, 25-$(OH)_2$D2-aminoalkyl, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.* Applicant is directed to the Revised Interim Guidelines for the

Examination of Patent Applications Under the 35 U.S.C. 112, ¶1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –
(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-5, 11 and 20 are rejected under 35 U.S.C. 102(a) as being anticipated by Kobayashi *et al* (of record, Analytical Biochemistry 244: 374-383, Jan 1997; PTO 892).

Kobayashi *et al* teach a conjugate comprising at least one vitamin D moiety such as 1,25(OH)2D3 conjugated to a target molecule moiety such as BSA having an affinity for plasma (See Fig 1, page 375 column 2, last paragraph, page 375 column 1, in particular) via a connecting group such as chemical bridge or bond at the C-11 α position (See Fig 1, in particular) or a connecting group such as N- hydroxy-succinimidyl ester which is a bifunctional connector to form a bond between said vitamin D and BSA (See page 375, third full paragraph, in particular). Claim 2 is included in this rejection because the vitamin D moiety is conjugated to the target molecule moiety, which is 1:1 ratio. Claim 11 is included in this rejection because N-hydroxy-succinimidyl ester is a good reagent for reaction with Lysine, which is an amino acid that forms an amide linkage through α-amino group or the ε aliphatic amino group. In addition, the N-hydroxy-succinimidyl ester reacts with the carboxyl group or thiol group of Cysteine amino acid residue that can be chelated. Claim 20 is included in this rejection because the reference teaches the reference conjugate in isotonic saline for injection, which is a suitable pharmaceutically acceptable carrier. Thus, the reference teachings anticipate the claimed invention.

7. Claims 1-4 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No. 4,292,250 (Sept 1981, PTO 892).

The '250 patent teaches a conjugate comprising at least one vitamin D moiety such as 25 hydroxy vitamin D2 and its derivatives conjugated to a target molecule moiety such as glucuronide wherein the glucoronide is linked to said vitamin D moiety at a position on the vitamin D moiety which is C-25 at a 1:1 ratio via a connecting group that form a bond between them. The reference glucoronide targets the vitamin D to the plasma. The '250 patent teaches the reference conjugate by virtual of its similarity to 25 hydroxy vitamin D2, which is a known biologically potent compound can be substitute for 25 hydroxy vitamin D2 in various therapeutic applications and particularly where the water solubility of the glucuronic acid compound is a necessity or advantage (See abstract, in particular). The reference conjugates offers additional advantages in that it is water-soluble and hence lends itself to intravenous and intramuscular dosage formulations and to administering to patients who have difficulty in assimilating lipids (See column 1, lines 65-68, in particular). Thus, the reference teachings anticipate the claimed invention.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 6, 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kobayashi *et al* (of record, Analytical Biochemistry 244: 374-383, Jan 1997; PTO 892) or US Pat No. 4,292,250 (Sept 1981, PTO 892) each in view of US Pat No. 5,576,309 (Nov 1996, PTO 892).

The teachings of Kobayashi *et al* and the '250 patent have been discussed supra.

The claimed invention as recited in claim 6 differs from the references only by the recitation of the vitamin D moiety is associated with the target molecule via the connecting group and at least one additional connective group.

The claimed invention as recited in claim 17 differs from the references only by the recitation of the conjugate further comprising at least one therapeutic agent other than a vitamin D moiety conjugated therewith.

The claimed invention as recited in claim 18 differs from the references only by the recitation of the conjugate wherein the therapeutic agent is a bone-therapeutic agent such as conjugated estrogens or their equivalents.

The '309 patent teaches 18 types of various estradiol derivative conjugates to a drug such as chlorambucil at the 3, 17 OH group (See Table 9-10, columns 22-23, column 5, lines 25,-44, in particular) and is useful for a pharmaceutical composition for treating tumor (See claims of '309, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to conjugate at least one therapeutic agent such as the estradiol derivative conjugates as taught by the '309 patent to the vitamin D conjugate linked through the C-11α position as taught by Kobayashi *et al* or the C-25 position as taught by the '250 patent. The recitation of one additional connective group is an obvious variation of the connective group as taught by Kobayashi *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '309 patent teaches 18 types of various estradiol derivative conjugates to a drug such as chlorambucil at the 3, 17 OH group (See Table 9-10, columns 22-23, column 5, lines 25,-44, in particular) and is useful for a pharmaceutical composition for treating tumor (See claims of '309, in particular). The '250 patent teaches the reference conjugate by virtual of its similarity to 25 hydroxy vitamin D2, which is a known biologically potent compound can be substitute for 25 hydroxy vitamin D2 in various therapeutic applications, particularly where the water

solubility of the glucuronic acid compound is a necessity or advantage (See abstract, in particular). Kobayashi *et al* teach vitamin D moiety such as 1,25(OH)2D3 can be conjugated to any target molecule moiety via a connecting group such as chemical bridge or bond or a connecting group such as N-succinimidyl ester at the 11 α position (See Fig 1, page 375 column 2, last paragraph, page 375 column 1, in particular).

11. Claims 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kobayashi *et al* (of record, Analytical Biochemistry 244: 374-383, Jan 1997; PTO 892) or US Pat No. 4,292,250 (Sept 1981, PTO 892) each in view of US Pat No. 6,309,666 (Oct 2001, PTO 892).

The teachings of Kobayashi *et al* and the '250 patent have been discussed supra.

The claimed invention as recited in claim 21 differs from the references only by the recitation of the pharmaceutical composition further comprising a differentially degradable coating encapsulating the conjugate for time release delivery of the conjugate.

The claimed invention as recited in claim 22 differs from the references only by the recitation of the pharmaceutical composition wherein said coating is an enteric coating.

The '666 patent teaches a pharmaceutical preparation in the form of a coated capsule such as enteric coating such as gelatin polymer capsule for time release delivery of any kind of medicament such as prednisolone (See entire document, abstract, column 6 lines 66-67 bridging column 7, lines 1-7, column 20, lines 25, in particular). The '666 patent teaches the time period from the discharge of the pharmaceutical preparation from the stomach till the contents of the hard capsule start to be released can be controlled to any length by selecting the kind and/or amount of polymer(s) used for a low pH soluble polymer film and/or the kind of the acidic substance (See column 3, lines 31-38, in particular). The reference pharmaceutical preparation has an advantage that the contents of the hard capsule can be released quickly and at any desired site of the lower part of the digestive tract (See column 3, lines 39-42, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the prednisolone in the polymer capsule for time release delivery as taught by the '666 patent for the conjugate as taught by Kobayashi *et al* and the '250 patent. From the combined teachings of the references, it is

apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '666 patent teaches that the enteric coating pharmaceutical preparation has an advantage that the contents of the hard capsule can be released quickly and at any desired site of the lower part of the digestive tract (See column 3, lines 39-42, in particular).

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

14. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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Art unit 1644
April 8, 2002

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